Summary of the AIDS Vaccine Research Working Group
Lausanne, Switzerland
September 1, 2004

Participants:
AVRWG Members

Barton F. Haynes, (chair)	Bette Korber
James Bradac, (Exec. Secretary)	Neal Nathanson
Emilio A. Emini	Douglas D. Richman
Scott Hammer	Jerald Sadoff
Stephen C. Harrison	Steven Wakefield

Ex-Officio Members

Lawrence Corey	Alan Greenberg
Gary Nabel	

NIH

Peggy Johnston	Bonnie Mathieson
Jorge Flores	

Drs. Haynes and Johnston thanked and presented certificates to the three members who are rotating off the committee: Neal Nathanson, Douglas Richman, and Stephen Harrison.

IAVI Strategic Plan – Emilio Emini

Emilio Emini presented IAVI's Research and Development Strategic Plan which includes In-Country Planning, Vaccine Acceptance Policy, and Country and Regional Planning. Most of the presentation centered on IVAI's Vaccine Development Program portfolio of DNA, MVA's, AAV, alphavirus (semliki forest), and adenovirus.

Based on the disappointing Phase I vaccine (IAVI 006 – clade A gag DNA prime, MVA boost) results IAVI will place the program on hold and may consider terminating the project when the results of their 009 and 010 trials are unblended. A final decision is expected in the 1st or 2nd quarter of 2005. The termination decision will also affect the DNA/MVA matched RENTA construct as well. Dr. Emini stressed that this trial was an "immunogen failure" and the MVA platform strategy may still be viable.

IAVIs Other Programs

Mutigene MVA based on the India clade C subgroup in development with Therion There has been some delay caused by invalid preclinical toxicity test and "instability" of the env gene. Instability problem is a process problem the inserts are different from the HIV A and the in vitro expresses is better. A Phase I trial is planned for India in 2005 and will shed light on the MVA platform issue.

Matched DNA prime/ MVA boost with Aaron Diamond Aids Research Center manufactured by IDT (Impfstoffwerk Dessau-Tornau GmbH). The vaccine contains two

plasmids encoding genes from an HIV subtype C isolate (China CRF_07) gag and env genes contained in one DNA plasmid, and pol, nef and tat genes in a second plasmid and is boosted by a matched MVA. The last volunteer has been enrolled in the DNA Phase I trial and the filling for the MVA is expected by late 9/04. The MVA Phase I is set to begin by the end of 2004.

All other IAVI MVA process development has been placed on hold.
With Bioption IVAI is developing a replication defective semliki forest virus particle vector. The immunogenicity is being evaluated in Chinese macaques and the data is expected by 11/04.

A recombinant adeno-associated viral vector (rAAV2) named tgAAC09 is being developed with Phil Johnson of the Columbus Children's Research Institute and Targeted Genetics. tgAAC09, a Clade C gag, protease, pol and env is codon optimized and different from most other AIDS vaccine candidates now in trials in that it is potentially a single-shot vaccine, rather than one that would require multiple injections over time. Data from a Phase I single inoculation dose escalation study in Europe is expected by Q1 05. Additional Phase I studies will be done in Africa and India with an effort to determine the effect of pre-existing immunity on the AAV vector. There was discussion about the potential regulatory problems of integration and that this was not the main concern since AAV DNA integrates at the same rate as plasmid DNA. The main regulatory concern is the fact that the vector is grown in HeLa cells, and while the final product is not tumorgenic Vero would be the cell of choice but this has to be weighed against the decrease in yield.

Future work will involve using AAV 1 as the vector since it has been shown to be more immunogenic in monkeys and presumably humans. There are also plans of using an AAV prime and Adeno boost in conjunction with Merck.

There was a discussion of IAVI efforts to establish study site for efficacy and immunology in Kenya, Uganda, Rwanda, and Zambia. These will involve the following protocols:

- Prevalence
- Incidence
- Capacity for rapid recruitment and effective retention
- Genotyping viruses responsible for new infections
- Nature of initial immune response to new infections
- Determine value ranges for reference labs in country (have been using values generated in the West and have found variable values for different populations)

A new Research and Design Consortium, headed by Ron Desrosiers with the focus on mechanism for protection from SIV, will be awarded by IAVI in the near future.

RV144 A Phase III Efficacy Trial Update - Jorge Flores

Background
RV144 Vaccine Trial Design

(16,000 healthy Thai volunteers, vaccine:placebo = 1:1)

Number	Week 0	Week 4	Week 12	Week 24
8,000	ALVAC Placebo	ALVAC Placebo	ALVAC Placebo + AIDSVAX Placebo	ALVAC Placebo + AIDSVAX Placebo
8,000	ALVAC vCP1521	ALVAC vCP1521	ALVAC vCP1521 + AIDSVAX gp120 B/E	ALVAC vCP1521 + AIDSVAX gp120 B/E

As of the 3rd week of August 2004, 8319 volunteers have been screened and 4974 have been enrolled.

The primary endpoint for the trial is acquisition of HIV infection.
To determine whether immunizations with an integrated combination of ALVAC-HIV (vCP1521) boosted by AIDSVAX® gp120 B/E prevent HIV infection in healthy Thai volunteers.

Secondary Endpoints:

- Changes in HIV-1 Viral Load To determine if the vaccine combination results in reduced HIV viral load "set point" among those acquiring HIV-1 infection. The trial is powered to detect a 0.5 log difference in viral load between vaccine and placebo recipients comparing vaccine recipients to placebo recipients.
- Changes in CD4 Cell Count To determine if the vaccine combination results in an increased CD4 count measured at viral load "set point" among those acquiring HIV-1 infection. The trial is powered to detect a 35% difference in CD4 count between vaccine and placebo groups comparing vaccine recipients to placebo recipients.
- Safety Reactogenicity and the frequency of local and systemic reactions (both AEs and SAEs) will be compared between vaccine and placebo groups .
- Risk behavior Volunteers may believe that the vaccine is protective against HIV infection and therefore modify their behavior in such a way that they increase their risk of exposure to HIV

Following John McNeil's presentation at the January 2004 AVRWG meeting a subcommittee of Scott Hammer, Larry Corey, Jerry Sadoff, and Steve Self (ad hoc) was formed to review the protocol and advise NIAID and the USMHRP as to how, if at all, the trial could be strengthened to "learn as much as possible." Their recommendations were presented at the May 2004 AVRWG meeting and are the following:

Primary Recommendation: Make amelioration of infection objective co-primary with acquisition. Strongly consider reducing sample size if seroincidence estimate is reliable.

After discussions between Thailand, USMHRP, and DAIDS the response to these recommendations was presented Dr Flores. The team agrees with the suggestion and will elevate the viral load objective to the primary analysis. Success will be claimed if a difference is detected either on infection or viremia control. However, the trial size (16,000 volunteers) would also stay the same since it was calculated to:

- Ascertain acquisition efficacy at the proposed power

- Overcome an increase in the type1 error rate
- Provide an adequate number of infected patients for a subsequent analysis
- As a safeguard for a decrease in infectivity rate.

With a sample size of 16,000 the trial has a power of 90.8% to detect a difference at the 0.05 level if true vaccine efficacy is 50% after full immunization and a >90% power to detect a 1 log difference in viral load. Incorporation of "viremia" end-point into primary analysis will result in an expansion of the experiment-wise error rate control with a two tailed 1% Type 1 error. Develop specific criteria for analyzing viremic endpoint and revise analysis plan accordingly e.g., time post-acquisition

Secondary Recommendations

1. Develop immunogenicity data in real time and supply to DSMB as background information

Team response: Agreed. Data in 200-300 vaccinees and 100 controls would provide information on activity of vaccine during the trial (should concentrate on T cell responses). The data provided to the DSMB should be used for background and not part of any stopping guideline

2. Consider developing criteria for operational futility Team response: Agreed
3. Above made with full appreciation of complexity involved in revising the protocol, including:
   - Reconsenting volunteers
   - Sponsor considerations
   - Relations with Thai colleagues
   - Multiple levels of review

Team response: Discussions are underway with IRBs, Department of Defense and Minster of Public Health to maintain power of acquisition analysis. Thailand's National Vaccine Committee is being consulted. There is a concern about potential negative impact from the trial.

Dr Flores described a revamped RV152 that would enroll patients with breakthrough infections from RV144.
RV152 would extend clinical follow-up of breakthrough infections:

- Primary objective: test for differences between infected subjects receiving vaccine versus placebo.
- Determine if surrogate biomarkers predicted disease progression
- Composite of key clinical endpoints (AIDS-defining events, initiation of antiretroviral therapy), and biomarker-based components (CD4 counts, plasma viral RNA measurements)
- Power calculations: event-based at pre-determined information milestone(s). Given VEs=0 in the parent RV144 study (65 vaccine/65 placebo infections, if true VEp=50%, 99 events (39 in the vaccine group) are needed to establish statistical significance.